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Impact of diabetes on uric acid and its relationship with the extent of coronary artery disease and platelet aggregation: A single-centre cohort study

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ABSTRACT

Background. Serum uric acid (SUA) elevation has been associated with the main determinants of atherosclerosis and metabolic syndrome, although an independent relationship between SUA and coronary artery disease (CAD) has never been confirmed. Recent reports suggested a central role of SUA in diabetic patients, possibly being an early marker of impaired glucose metabolism and best predicting the risk of cardiovascular events in these patients. Aim of current study was to evaluate the relationship between diabetes and uric acid and its association with the extent of CAD and platelet aggregation among diabetics.

Methods. In diabetic patients undergoing coronary angiography, fasting samples were collected for uric acid levels assessment. Coronary disease was defined for at least 1 vessel stenosis > 50% as evaluated by QCA.

Results. Diabetes was observed in 1173 out of 3280 (35.7%) diabetes was related to age, hypercholesterolemia, hypertension, BMI, renal failure, previous MI or coronary revascularization ($p < 0.001$, respectively) and smoking ($p = 0.001$). Diabetics were more frequently treated with ACE-inhibitors, ARBs, b-blockers, calcium-antagonists, diuretics, statins ($p < 0.001$, respectively), and ASA ($p = 0.004$). Diabetics displayed higher glycemia and HbA1c ($p < 0.001$), higher creatinine and triglycerides ($p < 0.001$) but lower total and HDL cholesterol ($p < 0.001$) and haemoglobin ($p < 0.001$).

No significant difference was found in SUA levels between diabetic and non diabetic patients ($p = 0.09$). In fact, we identified age, renal failure, hypertension, smoking, BMI, use of diuretics, statins, haemoglobin, triglycerides and HDL cholesterol levels as independent predictors of higher levels of uric acid (3rd tertile, ≥ 6.7 mg/dl or 0.39 mmol/l).

Among diabetic patients, no relationship was found between uric acid and the extent of coronary artery disease ($p = 0.27$; adjusted OR [95%CI] = 0.93 [0.76-1.1], $p = 0.48$), or severe

Abbreviations: CAD, Coronary artery disease; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; HDL, high density lipoproteins; MI, myocardial infarction; CVA, cerebrovascular accident; LV, left ventricle; EF, ejection fraction; ARB, angiotensin receptor blockers; LAD, Left descending coronary artery; CX, Circumflex coronary artery; RCA, Right coronary artery.

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(LM-trivessel) CAD (P = 0.05; adjusted OR [95%CI] = 1.01 [0.86-1.18], p = 0.94). Furthermore, SUA levels did not influence platelet aggregation.

Conclusion. Ageing, BMI, renal failure, hypertension, smoking, use of statins and diuretics, haemoglobin, HDL cholesterol and tryglicerides levels but not diabetes or glycemic control are independent predictors of hyperuricemia. Among diabetic patients, higher SUA is not independently associated with the extent of CAD or with platelet aggregation.

1. Background

Cardiovascular disease represents the leading cause of mortality in developed countries. Despite the great reduction in mortality achieved by the improvement in myocardial revascularization techniques [1,2], the results are still unsatisfactory in high-risk subgroups, especially in diabetic patients [3,4]. Therefore, much interest has been recently focused on the identification of new risk factors for CAD and its prevention.

Serum uric acid (SUA), a degradation metabolite of purines, has been extensively addressed in the past years as a possible risk factor for cardiovascular disease [5–7]. In fact, hyperuricemia has been associated with higher mortality and higher rate of cardiovascular events, as it might promote atherosclerosis progression by inducing oxidative stress, endothelial dysfunction and smooth muscle cells proliferation [8–11]. However, till now contrasting results have been reported on SUA as an independent predictor of cardiovascular disease. On the contrary, a stronger relationship has been found between SUA and main determinants of coronary artery disease (CAD), such as hypertension and metabolic disorders, and more recently, with diabetes mellitus [12,13]. A number of cohort studies and a subsequent meta-analysis, in fact, have assessed the association of SUA levels with the incidence of IFG and T2DM, suggesting hyperuricemia to be an early indicator of impaired glucose control, thus possibly allowing to identify those patients at higher cardiovascular risk [14–17].

We previously found no association between SUA and the extent of CAD [18], although different findings could be expected in diabetic patients, where contrasting results have been reported so far. In fact, the National Health and Nutrition Examination Survey III Linked Mortality Study (NHANES III) showed that baseline serum SUA level significantly predicted all-cause mortality only in patients with diabetes [19], while a recent longitudinal study including 1268 diabetics reported no association between baseline SUA level and all-cause or cardiovascular mortality at an extended 10 years follow-up [20].

Therefore, aims of the current study were to evaluate whether: 1) diabetes or glycaemic control are independently associated with elevated SUA; 2) SUA is associated with the extent of CAD and platelet aggregation among diabetic patients.

2. Methods

Our population is represented by a consecutive cohort of patients undergoing coronary angiography at Azienda Ospedaliera-Universitaria, “Maggiore della Carità”, Novara, Italy from March 2007 to October 2012.

All demographic and clinical data were collected after obtaining written informed consent from the patient and included in a dedicated database, in adherence to rules for protection of human subjects. No exclusion criteria were applied. Hypertension was defined as systolic pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or if the individual was taking antihypertensive medications. The diagnosis of diabetes was based on previous history of diabetes treated with or without drugs, fasting glycaemia > 126 mg/dL, random glycaemia > 200 mg/dL or HbA1c > 6.5%. Acute Coronary Syndrome was defined as an elevation of cardiac biomarkers beyond the upper limit of normal (ULN) (respectively 0,04 μg/l for Troponin I and 5,0 μg/l for CK-MB) due to angiographically documented critical coronary stenosis (>70%).

2.1. *Biochemical measurements*

Blood samples were drawn at admission in patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, uric acid, blood cells count and lipid profile were determined by standard methods. Cardiac biomarkers (Troponin I and CK-MB) were assessed by sandwich immunoassay with direct chemiluminescence [21].

2.2. *Coronary angiography*

Coronary angiography was routinely performed, preferring a radial approach, using 6-French right and left heart catheters. Quantitative coronary angiography was performed by experienced interventional cardiologists by automatic edge-detection systems (Siemens Acom Quantcor QCA, Erlangen, Germany) as previously described [22]. After the visual inspection of the coronary artery, the frame of optimal clarity was selected, showing lesion at maximal narrowing and arterial silhouette in sharpest focus. After the calibration of guiding catheter, analysed arterial segment with coronary lesion was defined by moving the cursor from the proximal to the distal part of coronary artery to ensure adequate determination of reference diameter. We measured minimal luminal diameter, reference diameter, percent diameter stenosis, and length of the lesion.

Significant coronary artery disease was defined as at least 1 coronary stenosis more than 50%. Severe coronary disease was defined as three-vessel disease and/or left main disease. For patients who had previously undergone a percutaneous coronary intervention, even though no restenosis was observed, the treated vessel was counted as significantly diseased. In previously bypassed patients, native arteries